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NUTRITION REVIEWS

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May 1953

Special Article

Nutrition in Clinical Medicine 129

Clinical Nutrition

Subcutaneous Fat 131
Serum Iron in Liver Disease 134
Isotopic Measurement of Protein Absorption 136
Body Composition in Health and Disease 137
Tyrosine Metabolism on Low Ascorbic Acid Intakes 141
Intestinal Paralysis Produced by Decreased Intracellular Potassium 142
Obesity, Weight Reduction and Longevity 144

Animal Nutrition

Combined Deficiency of Vitamin B_{12} and Folacin in Swine 146

Experimental Nutrition

Dietary Fat for Reproduction and Lactation 147
The Need for Certain Amino Acids Following Hemorrhage 148
Adrenocortical Function in Monkeys with Scurvy 150
Hypercholesterolemia with Failure to Induce Atherosclerosis in the Rat 152
Glycogen 154
Protein Intake and Starvation-Induced Endocrine Involution 156
Cholesterol Synthesis from Acetate in Diabetes 158

Notes

Letters to the Editor 159
Third Survey of Food and Nutrition Research in the United States. 160

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NUTRITION REVIEWS

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NUTRITION IN CLINICAL MEDICINE

The importance of maintaining a good state of nutrition in aiding the recovery of the sick patient has been recognized intuitively by physicians for many centuries. An outstanding exception to this general rule, however, was the practice of "starving" the patient suffering from typhoid fever, the error of which was ultimately recognized. Despite this early appreciation of the value of supplying the patient with an adequate diet, the recognition of nutritional deficiencies and practical means of overcoming these has only become an important branch of clinical medicine in recent decades.

The discovery of vitamins, and the recognition that such scourges of mankind as pellagra, beriberi, rickets and scurvy were due to vitamin deficiency, have led to the practical eradication of these formerly common disorders. By the use of foodstuffs containing the vitamins responsible for these disorders, the occurrence of avitaminoses may be prevented. The subclinical forms of vitamin deficiencies are also now recognizable and amenable to therapy. The role of ascorbic acid in the pathogenesis of certain forms of anemia, of vitamin D in osteomalacia (adult rickets) and of vitamin B_{12} in pernicious anemia are examples of disorders responsive to vitamin therapy. The future may disclose other clinical states due to deficiencies of other vitamins, the functions of which in the organism have only recently been disclosed.

The maintenance of a normal state of nutrition requires the administration of a diet adequate in caloric content as well as in its composition. Much attention is being given now to the problem of supplying a sufficient number of calories to the ill individual in order to depress the rate of destruction of his own body proteins to supply the caloric requirement which may be greatly increased over normal. This is often difficult in the sick patient whose appetite is fickle and whose capacity to ingest an adequate amount of food is impaired by his illness. For the patient capable of taking food by mouth, the use of high caloric formulas makes possible the administration of a diet adequate in caloric content. For this purpose special preparations such as protein and amino-acid concentrates are widely used as sources of vital protein. Oral fat emulsions serve as high caloric supplements which are easily administered and well tolerated (F. J. Stare, *Ann. N. Y. Acad. Sci.* **56**, *3 (1952)*). Preparations consisting of highly emulsified edible oil (40 per cent) and glucose (10 per cent) have been introduced commercially and are finding increasing application. These preparations which provide about 150 calories per ounce are palatable since the small size of the emulsified oil deprives it of its oleagenous taste. They are well utilized and impose no excessive burden on the digestive system.

An important field of application of nutrition in clinical medicine has resulted from the recognition of the role played by the nutrients in the maintenance of the functional integrity of the organism. Not only are the vitamins necessary for the elaboration of basic enzyme systems essential for the activity of the cells, but a lack of an ample supply of protein of good quality will also result in devastating effects. So-called "hunger edema" observed in malnourished peoples, and "kwashiorkor," a similar condition observed in India and Africa, are examples of such deficiencies. Of more practical importance in everyday practice are the milder forms of a similar

deficiency which gives rise to chronic disability without the striking symptoms seen in more extreme deficiencies.

Of the specific disorders in which high protein feeding plays an important role in prophylaxis and therapy may be mentioned portal cirrhosis of the liver and toxemia of pregnancy. The dietary management of cirrhosis of the liver has resulted in a striking improvement in the prognosis of this disease and constitutes the mainstay of modern therapy. It is dependent on the administration of large amounts of proteins and vitamins which exert a lipotropic action. Although the etiologies of eclampsia and other toxemias of pregnancy are not established and may be multiple in origin, it is generally believed that they are associated with poor nutrition and the availability of sufficient protein of good quality is therefore advocated as a prophylaxis against the development of these serious complications.

As a result of the elucidation of the role of electrolytes and water in the animal economy, increasing attention is being given to the importance of regulating the intake of the inorganic salts and water in a variety of disorders. The primary role of the retention of sodium chloride in the pathogenesis of edema has led to the restriction of salt intake in the management of the edema of cardiac and renal disease and the ascites of hepatic cirrhosis. The drastic restriction of sodium in the management of hypertensive cardiovascular disease is also now an established procedure. In the patient suffering from Addison's disease, the administration of sodium chloride and the restriction of potassium constitutes a basic principle of therapy.

An evaluation of the salt and water requirements is of vital importance in every seriously ill patient, particularly those in whom as a result of disability, renal disturbance, or losses from the gastrointestinal tract the normal electrolyte-water balance is disturbed. As further knowledge of the alterations in electrolyte-water balance in disease has been acquired, the importance of regulating the intake of the inorganic constituents of the diet has expanded. Thus the importance of potassium salts in certain patients recovering from diabetic acidosis has received much attention during recent years, although the administration of sodium chloride infusions to overcome the extracellular volume deficit in this condition has long been practiced. Likewise, an understanding of the fundamental defect in acute renal failure has led to the use of an electrolyte-free diet as an important part in the management of this formerly highly fatal condition.

One of the outstanding problems of present-day research in medicine is the prevention, if possible, of the so-called degenerative diseases, particularly arteriosclerosis and hypertensive cardiovascular disease. With the great advances in the management of the infectious disorders and the increased life-expectancy, these disorders and malignancy constitute the greatest causes of death and disability in an ever-increasing part of the population. Considerable attention has been given in recent years to the role of diet in the pathogenesis of arteriosclerosis. The role of cholesterol in this process is problematic as is also the possibility of influencing the course of the disorder by limitation of the cholesterol intake. Better established is the beneficent role played by caloric restriction generally in the management of cardiac disease and diabetes.

Recognition of the role of the rare elements in the animal economy has led to several practical applications. By the administration of iodine in the form of iodized salt or as a supplementary feeding several times yearly satisfactory prophylaxis against endemic goiter has been made possible. The use of iron in certain anemias is well-known. The addition of fluoride to communal water supplies as a preventive of dental caries is gradually being extended.

Although instances of disease due to lack of minerals is well known in agriculture, such deficiencies have not been demonstrated to play a role in known disorders of the human being.

It will be evident from this brief review that nutrition plays an important role in clinical medicine. It may indeed be said that in no diseased condition can the physician afford not to apply the knowledge gained in recent experimental studies to the patient's care. In many cases, this can prove life-saving; in others, it may markedly shorten the period of disability. Much remains to be done, particularly in the field of prophylaxis against the degenerative disorders. The recent demonstration that a relatively short period of choline deficiency in the immature rat causes renal damage which eventuates in the development of hypertension later in the animal's life has raised the question whether a comparable deficiency during childhood may be responsible, at times, for the appearance of this disorder in man. The materials which make up the living organism as well as the multitudinous reactions which constitute life are dependent entirely on the nutrients taken in the diet, and it is not surprising, therefore, that nutrition should play so important a role in health and disease. With each advance in our knowledge of the broad field of nutrition as well as of metabolism and its other allied sciences, further applications of nutrition in the management and prevention of disease are revealed.

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SUBCUTANEOUS FAT

It has been generally believed that human subcutaneous fat, showing wide quantitative variations in different states of nutrition, serves as an effective insulator. Strangely enough, until recently, actual measurements of the thermal conductivity of human adipose tissue have apparently not been available. Using a thermoelectric heat-flow disk, (H. S. Hatfield and F. J. Wilson, *J. Sci. Instr.* **27,** *1 (1950)*; Hatfield, *J. Physiol.* **111,** *10P (1950)*); Hatfield and L. G. C. Pugh, *Nature* **168,** *918 (1951)*) examined several specimens of human adipose and muscle tissues, as well as some beef tissues. The human specimens were obtained from hospital postmortem dissections. On the average, the thermal conductivity of the human fat was about one-half the value for human muscle, thus confirming the idea that fat is a better thermal insulator. The authors have noted that excised fat retains fairly well its conductivity characteristics, even when kept for one or two days at room temperature, while muscle shows large changes (an increase) in thermal conductivity.

Several papers on subcutaneous fat, measured by skinfold calipers, were contributed by D. A. W. Edwards. In the initial study (*Clin. Sci.* **9,** *259 (1950)*) the method was described and the pattern of distribution of subcutaneous fat was examined on the basis of measurements made at 53 sites. The skinfold measurements were corrected for the thickness of the skin proper; the latter values had been obtained for each of the 53 sites in 8 female cadavers. In an average-weight young woman (148 pounds) large fat depots were found around the shoulders (mean fatfold thickness of 30.2 mm.), base of neck (16.5 mm.), back (17.8 mm.), abdomen (24.8 mm.), and upper thigh (38.3 mm.). On going from underweight (110 pounds) to overweight (180 pounds) individuals, at the "standard" height of 64 inches, the increases in fatfold

thickness at the different sites varied from 5 to 37 mm. When the increase for each site is expressed as percentage of the fatfold thickness of individuals of *average* weight (148 pounds), the values vary less, but the spread is not inconsiderable (from about 60 to 160 per cent). This indicates that different sites vary in their share of the newly deposited fat. In individual patients on reducing diets both the values for the "total" fat (based on all 53 sites) and for individual sites decreased during weight losses parallel to the group trends.

The next study (D. A. W. Edwards, *Clin. Sci.* **10,** *305 (1951)*) was concerned with the sex and age differences in the distribution of subcutaneous fat. The pattern was calculated by expressing the sum of the fatfold thicknesses in four body areas (anterior and posterolateral trunk, arm, and leg) as percentage of the total of the fold thicknesses at 53 sites. Before puberty the pattern was identical in both sexes. After puberty in males there was a relative increase in the fat deposited on the trunk, especially on its posterior and lateral surface, and a relative decrease at the extremities, especially at the legs. In the females the changes in fat distribution were much less striking. In contrast to men, the fat deposits at the leg showed a relative increase. This trend was reversed in menopausal women, but the adult females at all ages had more fat on their legs, in proportion to the total amount of fat, than the men (33.6 per cent in premenopausal women, 24.8 per cent in men).

In addition to these relative values, the averages of all fold thicknesses in a subgroup of individuals of approximately standard weight for height are of interest. The sex difference was present between boys and girls (mean values of 5.8 versus 13.0 mm.), and young men and women (7.8 versus 12.1 mm.). The age trends during maturity were not studied systematically. The average for menopausal and postmenopausal women, of unspecified age, showed some decrement (mean of 11.7 mm.) in subcutaneous fat.

The use of skinfold measurements in a study of changes in body fat during subsistence on survival rations was reported by R. W. Newman ("Measurement of Body Fat in Stress Situations," *Rep. No. 193, Quartermaster Climatic Research Laboratory, Lawrence, Mass. (1952)*). Skinfolds were measured by calipers activated by a flat spring. Three sites were used (chest, waist, and upper arm). In order to eliminate the variation in skinfold values due to minor differences in locating each skinfold in successive measurements, the sites were marked by injecting minute amounts of sterile india ink under the skin. Two points were thus marked at each site, identifying the width of the skin to be lifted in the form of a fold. In longitudinal studies made on a small group of individuals such precautions definitely increase the reliability of day-to-day measurements. From the three skinfolds the value of total ("nonessential") body fat was calculated using the equations developed by J. Brozek and A. Keys (*Brit. J. Nutrition* **5,** *194 (1951)*) on the basis of correlation between skinfold measurements and specific gravity values.

There were 10 men in the survival-ration study. During the thirteen days of the control period the subjects were fed on C-rations which provided, theoretically, 3300 calories. The ration was not consumed *in toto*, with the actual caloric intake being about 3000 calories. Toward the end of this period the novelty of the C-ration was wearing off and the tedium of subject duties and life in close quarters began to be reflected in the relative lack of interest in food. The survival ration, fed for ten days, contained 900 calories and was consumed completely by all subjects.

On the experimental days the water intake was 800 cc. per day, as compared with the voluntary intake of about 2500 cc. on the control days. In the control period, the body weight showed a slight

average decrement (from about 146 to 144 pounds), while the estimated body fat decreased from 9.2 to 8.8 per cent. At the end of the ten-day experimental period the body weight decreased to 135 pounds and the fat reached the level of 5.8 per cent of body weight. The weight loss of 10.1 pounds, calculated from the eighth day of the control period to the end of the experimental period, was accounted for by the loss of fat (5.4 pounds), water associated with fat ($5.4 \times 0.2 = 1.1$ pounds), protein estimated from the nitrogen balance studies (0.7 pounds of anhydrous protein), and water associated with protein ($0.7 \times 4 = 2.8$ pounds). The four components added together equal 10.0 pounds. In fundamental studies on the effects of caloric imbalance more direct methods for the characterization of changes in body composition, including total body water and its principal fractions, would be desirable. In the present investigation, the estimates of the fat content from skinfolds seem to have been useful in the breakdown of the weight loss.

Another study reported from the same laboratory points out the limitations rather than the merits of the skinfold technic in studying changes in body composition in environmental stress situations. During the control period of three weeks the 5 subjects were kept in an air-conditioned room at about 75°F. During the two-week experimental period the day temperature was raised to 120°F., with 100°F. at night. During the terminal period of ten days the temperature was reduced to 75°F. The subjects were kept at a rigorous schedule of physical activity in order to maintain the energy expenditure at a uniform level (four thirty-minute periods of walking on a treadmill at 4 m.p.h. daily).

The caloric intake during the last two control weeks was about 2800 calories, while during the heat period the food consumption declined from 95 per cent of the ration offered to 76 per cent during the second week of the heat experiment. The average food consumption during the two weeks of the heat experiment was about 2500 calories. At the same time the average water intake rose from 2860 cc. per day at 75°F. to 9575 cc. in the heat. This amount was calculated to replace the sweat and urine losses.

During exposure to heat, the changes in body weight represent a combined effect of the degree of hydration and the loss of soft tissues. The weight showed a relatively small but continued decrement throughout the three phases of the study (preheat period, about 139.4 and 138.4 pounds; end of heat period, 137.0 pounds; end of postheat period, 133.0 pounds). The mean fat percentages calculated from skinfolds at beginning and end of the preheat period were 8.0 and 7.4, during the postheat period 7.0 and 6.1. These data make good sense. The strange but interesting phenomenon was the *increase* in the thickness of subcutaneous tissue during exposure to heat, resulting in an apparent elevation of the estimated fat content of the body (average value of 8.8 per cent of body weight). This spurious rise was observed on the first day of the heat period, remained throughout the two weeks of exposure to high environmental temperature, and disappeared just as suddenly on the first day of the postheat period. In interpreting the phenomenon, simultaneous data on the thickness of the subcutaneous fat plus skin, obtained from an x-ray (which does not require lifting of the skinfold) would be useful. It is probable that the thickness of the tissue has actually increased, due to the peripheral vasodilatation and, more importantly, to increased hydration of the tissues.

In a separate short-term investigation, in which the pre-experimental and post-experimental temperature and other experimental conditions were not so well controlled as in the main study, an increase in the thickness of the skinfolds was observed as early as the end of the first hour

in the hot room and reached the day's maximum in about three hours (10 per cent of the control value).

The data are useful in that they bring to light limitations of the skinfold technic for estimating man's fatness not previously reported in the literature. Fortunately, the error is not excessive, even at very high temperatures. Provided the increment is proportional to environmental temperature, a correction factor could be calculated. Also, it is likely that such changes are absent in thoroughly acclimatized subjects. In the study reported above the calculated fat was 9.1 per cent on the first day in a hot environment, and 8.6 on the twelfth day, as compared with 7.4 at the end of the preheat and 7.0 at the start of the postheat period.

The author concludes that, in the absence of heat stress, the estimation of the fat content of the body from skinfolds will yield satisfactory results in a variety of laboratory and field conditions. The simplicity of instrumentation and the ease of collecting data make the method ideal for investigating the leanness-fatness of larger groups, inaccessible to study by the more complex methods, based on specific gravity and total body water determinations.

SERUM IRON IN LIVER DISEASE

The absorption, metabolism and storage of iron have been extensively investigated in normal and diseased humans as well as in animals, but knowledge of this subject continues to expand. In a previous review (*Nutrition Reviews* **9,** *293 (1951)*) the function of the liver, spleen and reticuloendothelial system as depots for iron storage was emphasized. In view of the role of the liver as a storage depot, study of iron metabolism in patients with hepatic disease has been considered potentially valuable in determining the relationship of liver function and hemoglobin synthesis and destruction. In this regard, an investigation of the relationship of serum bilirubin and serum iron levels has been conducted in patients with hepatobiliary diseases by H. Ducci, A. Spoerer, and R. Katz (*Gastroenterology* **22,** *52 (1952)*).

These workers have reviewed previous reports indicating the existence of elevated serum iron values in patients with hepatitis and have extended their studies to include patients with cirrhosis and posthepatic (obstructive) jaundice in addition to those with hepatitis. In 62 patients with acute hepatitis serum iron and serum bilirubin values were determined on the same sample of blood. No correlation between these values was obtained, but comparison of serum iron levels with values obtained in 40 normal individuals (62 to 168 micrograms per cent, mean 108.4) revealed significant elevation in patients with hepatitis. Forty had values over 170 micrograms per cent, while only 2 patients had serum iron levels under 100 micrograms per cent and the remainder were between 100 and 170 micrograms per cent. By contrast, of 68 patients with cirrhosis only 11 had values over 100 micrograms per cent while none was over 200 micrograms per cent. Patients with posthepatic jaundice showed somewhat more widely distributed serum iron levels, with 13 of the 27 cases being under 100 micrograms per cent and 5 being over 200 micrograms per cent. Serial observations on 2 of these patients, however, revealed isolated values of 466 and 268 micrograms per cent. As in hepatitis, no correlation of serum bilirubin and serum iron was found in cirrhosis or posthepatic jaundice. Serial determinations in patients with hepatitis likewise failed to show correlation of the bilirubin and iron levels.

Although these results suggest a difference in serum iron values in patients with

hepatitis and other types of jaundice which may be of diagnostic assistance, they do not yield much information concerning the mechanisms involved. They do demonstrate, however, the fact that serum iron is probably controlled by factors which are unrelated to bilirubin formation or excretion.

Somewhat more extensive study of iron metabolism has been undertaken by S. E. Gitlow, M. R. Beyers, and J. P. Colmore (*J. Lab. Clin. Med.* **40,** *541 (1952)*), who have used the technic of intravenous iron tolerance tests. These investigators have previously reported their use of this method in normal subjects and in patients with hemochromatosis (Gitlow and Beyers, *J. Lab. Clin. Med.* **39,** *337 (1952)*). By the injection of 10 mg. of elemental iron in the form of green ferric ammonium citrate they have determined five- and one hundred and twenty-minute levels after injection in addition to fasting serum iron. In this technic the five-minute iron level represents the total iron binding capacity of the serum (TIBC), and the authors have made use of a ratio (DEC/INC) in which INC is the increase from the fasting level to the five-minute level (TIBC) and DEC is the fall in serum iron from the five-minute specimen to the one hundred and twenty-minute sample. This DEC/INC ratio is believed by the authors to represent the relative tissue uptake of iron from the serum.

Having determined from this procedure that a high DEC/INC ratio is characteristic of hemochromatosis as well as a normal or a high fasting serum iron, a normal or low total iron binding capacity (TIBC), and a high degree of saturation of iron binding protein, these workers subsequently studied patients with cirrhosis and hepatitis. Although the results in cirrhotic patients revealed a wide spread of individual values there was a definite tendency toward a low fasting serum iron, with 7 of the 21 patients having serum iron levels below the lowest limit of their normal range. Of these 7, however, 5 were noted to have active gastrointestinal bleeding at the time of study and 6 had an associated anemia. Thus, hypoferremia was associated with either bleeding or anemia in a high percentage of cases. Anemia was present in 3 other patients with normal serum iron levels, but these patients also had marked bromsulfalein retention. The latter was, in their experience, associated with normal or increased serum iron, suggesting that liver damage of the type yielding bromsulfalein retention elevates the serum iron. This finding is not borne out by a strict correlation of bromsulfalein with serum iron levels from the data, however.

Iron binding capacity (TIBC) of the serum was also depressed in patients with cirrhosis; in no case was it above normal, and in 8 the value was below the normal range. Nearly all of these also had low serum iron levels; included in this number were the patients with active bleeding mentioned previously. This low TIBC in cirrhosis is, however, in contrast to the usual finding of high TIBC values in uncomplicated blood loss or iron deficiency anemia (C. E. Rath and C. A. Finch, *J. Clin. Invest.* **28,** *79 (1949)*). The remainder of the test values in these studies, including saturation, one hundred and twenty-minute values and DEC/INC, showed no correlation with the disease or with other laboratory data.

Only 3 patients with hepatitis were studied and no valid conclusions could be drawn, but the data suggested a similarity between the results in this disease and those found in hemochromatosis. Two other patients with enlarged livers and diabetes showed no significant change in iron tolerance studies from normal subjects.

These investigations of Gitlow and coworkers reveal differences in iron tolerance between cirrhosis and hemochromatosis and are potentially helpful in the differential diagnosis of these two conditions. In addition, the studies confirm previous reports of the unexplained occurrence of

hypoferremia in some patients with cirrhosis and contribute evidence which indicates that a lowered iron binding capacity in cirrhosis is demonstrable with this technic. This low TIBC may contribute to the hypoferremia found in such patients, but unfortunately the frequent occurrence of bleeding limits the conclusions which can be drawn. The extension of these studies to include more patients without bleeding might perhaps determine the relative roles of lowered serum iron binding capacity and possible defects in hepatic function in producing hypoferremia. Since iron is bound as part of a protein complex in the serum this would appear to be a very likely possibility in view of the defects in protein synthesis which occur with liver damage.

Hyperferremia in hepatitis may be related to the release of iron from the liver as its cells are destroyed, but as yet the mechanism of hypoferremia in chronic liver disease such as cirrhosis remains obscure. It may be due to the defect in iron binding by the serum as mentioned above, but conclusive evidence is not yet available. Meanwhile it should be pointed out that the adrenal cortex may be involved since it has been shown that hypoferremia accompanies stimulation of this organ (*Nutrition Reviews* **9,** *250 (1951)*). Increased 11-oxysteroid excretion in the urine of patients with cirrhosis (A. M. Bongiovanni and W. J. Eisenmenger, *J. Clin. Endocrinol.* **11,** *152 (1950)*), suggesting increased adrenal cortical activity in this disease, has also been reported. On hypothetic grounds, hypoferremia in cirrhosis may be a result of adrenal cortical activity. Despite such associated findings, however, the vagaries of serum iron metabolism in cirrhosis must be considered unexplained.

ISOTOPIC MEASUREMENT OF PROTEIN ABSORPTION

Measurement of the absorption of protein foodstuffs requires the methodology of performing nitrogen balances. In studying gastrointestinal diseases such as fibrocystic disease of the pancreas (mucoviscidosis) in small children this method is not easily applied by those not equipped for extensive metabolic studies. Consequently a search for simpler methods has been made. The postalimentary rise in plasma amino acids has been suggested by C. D. West, J. L. Wilson, and R. Eyles (*Am. J. Dis. Child.* **72,** *251 (1946)*). More recently P. S. Lavik *et al.* (*Pediatrics* **10,** *667 (1952)*) have suggested the use of casein iodinated *in vitro* with radioactive iodine.

Approximately 1 microcurie of this radioactive casein per kilogram of body weight was mixed with enough carrier casein to supply 1.75 g. per kilogram of body weight in a suitably flavored mixture. Urine, blood and fecal specimens were collected at suitable intervals. Their radioactivity was measured by placing the fecal samples in a standard position in relation to a scintillation counter and comparing them with standards made up to the same volume. Urine and blood samples were counted with a liquid counter. The conventional methods of sample preparation and an end window counter were used when more precise results were desired.

The use of I^{131}-labeled casein in the study of protein absorption depends upon the validity of a number of assumptions. Since tyrosine is the only amino acid in casein which is labeled, information derived by this method is accurate only for the liberation of iodotyrosine from proteins and its subsequent distribution and metabolism. Generalizations from such information may not be warranted. Should radioiodine be liberated from iodotyrosine either before or after hydrolysis of the protein, the results

would become confusing. Abnormal thyroid function might be expected to interfere with the interpretation of the results.

Lavik and co-workers have performed a series of animal experiments designed to test these assumptions. The radioactive products formed following the digestion of iodinated casein incubated with digestive juices obtained from various levels of dog intestine previously stimulated by casein feeding were measured chromatographically. Less than 12 per cent of the radioactivity behaved as inorganic iodide after two hours of digestion, during which time most of the activity appeared in the fraction representing iodinated tyrosine. Depancreatized dogs were given casein labeled with I^{131} and the uptake of the isotope in the blood was measured and compared with the uptake by the same animals before operation. A much slower rise was found following removal of the pancreas and this was attributed to a deficiency in digestive enzymes with a less rapid liberation of labeled tyrosine.

Studies on 10 patients not having gastrointestinal disease and 5 patients diagnosed as having cystic fibrosis of the pancreas were then performed. These patients were given 4 to 10 drops of Lugol's solution twice daily for two days preceding the test, and for a subsequent period of four days, to block the thyroid uptake of I^{131}. The greatest difference between the two groups was found in the fecal excretion of radioactivity during a seventy-two-hour period following the test meal. Among the controls this excretion did not exceed 6 per cent of the administered dose. The children with pancreatic disease excreted between 10 and 40 per cent (average 22.5 per cent). The addition of pancreatin to the test meal reduced this excretion by one-half in 2 of the 4 patients so tested. A slower rise in radioactivity in blood and urine was found in the cases of pancreatic fibrosis, but the differences were not large enough to be of diagnostic significance.

This new approach to the study of the digestion and absorption of proteins should stimulate further exploration of its possible applications in clinical medicine. When applied to the study of defects as great as those reported by the present authors very clear-cut results can be obtained. The lack of diagnostic differences in blood uptake and urinary excretion of the isotope emphasizes the fact that only measurement of the unabsorbed moiety of the isotope gives data which may be reliably interpreted. Those investigators more familiar with the methods of isotope research than of quantitative biochemistry may prefer this approach to that of the possibly more laborious nitrogen balance. However, the latter method is more accurate and permits a more comprehensive measurement of nitrogen metabolism. Neither approach is essential for the clinical diagnosis of fibrocystic disease of the pancreas.

BODY COMPOSITION IN HEALTH AND DISEASE

The importance of a knowledge of body composition for the critical appraisal of nutritional status and metabolic changes has been stressed in a number of recent articles. Quantitatively, the greatest single component in the body is water. Its precise assessment is a necessary part of any study of body composition. The technics commonly used for its estimation have been previously reviewed (*Nutrition Reviews* **7**, *308* (*1949*); **9**, *265*, *299* (*1951*); **10**, *14*, *70*, *181*, *246* (*1952*)). Probably the most reliable clinically applicable method is the isotope dilution technic utilizing deuterium oxide as the tracer.

As a basis for a study of the changes in

total body composition in patients with various types of illnesses and injuries, I. S. Edelman *et al.* (*Surg. Gynec. Obstet.* **95,** *1* (*1952*)) determined total body water by the deuterium oxide technic in normal human beings of both sexes throughout the life span. One hundred and twenty measurements were made in volunteers covering an age range of 2 days to 86 years and a weight range of 2.3 to 100.3 kg. Measurements were made in the fasting state. All subjects were in good health and considered "normal." No changes in their daily routines and dietary habits were made. Nude heights and weights were obtained at the time of the injection of the deuterium oxide.

An indication of the reproducibility and validity of the deuterium oxide method was obtained by two measurements of total body water seven to one hundred and fifty-five days apart in each of 6 young adult individuals (5 males, 1 female). The differences between the two values in each pair of measurements varied from −2.4 to +1.6 liters. Changes in body weight during this same time varied from −3.7 to +3.1 kg. In terms of per cent of body weight, the body water was constant to within 2 per cent. In the one patient with a constant body weight, the difference in body water in two observations thirty days apart was 0.5 liters, or a variation of 1 per cent.

For purposes of comparison the 120 subjects were arbitrarily divided into 11 groups according to age and/or sex. Numerically, the largest groups studied were young adult males (34) and young adult females (18). In 6 infants 2 to 28 days of age, the total body water ranged from 72 to 83 per cent of the body weight and was, on the average, 77 per cent. This is the highest figure observed by Edelman *et al.* for any age group and is in keeping with the relatively increased extracellular space in normal newborn infants previously reported by other investigators (*Nutrition Reviews* **7,** *308* (*1949*)). The mean total body water fell to 63 per cent in a group of 9 infants 1 to 9 months of age, and to 59 per cent in a group of 11 children 1 to 9 years of age. Little change was thereafter observed in males until the fourth decade, at which age the mean body water fell to, and thereafter remained at, 55 per cent of the body weight. No difference attributable to sex was noted until the age of 16. Thereafter the mean total body water was lower in the females studied than in the males of corresponding ages.

These differences in total body water among adults of different ages and sex have been observed by others and are ascribed to variations in body fat content—the higher the proportion of body fat, the lower the percentage of body water. Adult females are generally fatter than males, and the elderly are usually fatter than younger individuals (*Nutrition Reviews* **9,** *265* (*1951*); **10,** *181*, *246* (*1952*)). In Edelman's study, the mean total body water of 34 males between 17 and 34 years of age was found to be 61 per cent of the body weight. Body fat calculated by the formula per cent fat = 100 − per cent water/0.732 (E. N. Rathbun and N. Pace, *J. Biol. Chem.* **158,** *667* (*1945*)) is 17 per cent of the body weight in this group. (The figure 0.732 refers to the water content of lean tissue and is assumed to be constant.) These values of measured body water and calculated body fat check closely with data obtained in healthy young males by measurements of specific gravity and calculation of body water. The mean body water in 18 young adult females of similar ages was found to be 51 per cent of the body weight (as compared to 61 per cent in males of similar ages) while the body fat calculated with the above formula is 30 per cent (as compared to 17 per cent in males of similar ages). In the groups of subjects over 57 years of age, the mean body water in 6 males was 54 per cent; in females, 46 per cent. The corresponding calculated figures for body fat were 26 per cent and 37 per cent respectively. Edelman and his co-

workers raise the question whether there is some other sex factor in addition to fat producing the male-female differential in total body water. They observed that the thin females among their subjects are significantly lower in water content than the males of the same thin build. They mention that a sex-linked variation in water content of lean tissue (ordinarily considered constant at 73.2 per cent) may account for this impression.

It should be mentioned that the calculation of body fat from measurements of body weight and body water is dependent not only on a constant proportion of water in the lean body tissue, but also on a constant ratio of extracellular:intracellular water. If this ratio is unusual, the calculation is subject to error. Thus, the percentage of body fat in the youngest infants (ages 2 to 28 days) calculated from the data of body weight and body water reported by Edelman is zero. This presumably low calculated figure is probably due in large part to the unusually high extracellular fluid content in infants of this age group. Similar errors may be anticipated in diseased states accompanied by marked disturbances in fluid balance.

Edelman *et al.* observed that where body weight is less than 20 kg., body water is a linear function of body weight. They mention that this relationship was also observed by B. J. Friis-Hansen, M. Holiday, T. Stapleton, and W. M. Wallace (*Pediatrics* **7,** *321* (*1951*)), who found the equation for this relation to be:

$$\text{Body water in liters} = 0.55 \times \text{wt. in kg.} + 0.51.$$

Among adults, deviations (greater in females) from this relationship are seen due presumably to variations in body fat.

Edelman *et al.* have also analyzed their data in terms of surface area. They observed that in children with a surface area of less than 1.0 square meter, the total body water is a linear function of surface area. As the surface area increased to 2.0 square meters, a similar relationship was observed among females, but adult males, by virtue of a higher muscle content per unit body weight, show a greater fraction of body water per unit body surface.

The reported data on total body water measured directly by desiccation in 17 human subjects of varying ages are tabulated in Edelman's paper. A discussion of some of these data has appeared recently (*Nutrition Reviews* **9,** *299* (*1951*); **10,** *14* (*1952*)). The abnormality of some of the chemically analyzed individuals has been pointed out, for example, 2 of the bodies analyzed were grossly edematous. Edelman *et al.* find a "surprisingly good agreement between many of these figures and our own data."

A second paper (F. D. Moore *et al.*, *Surg. Gynec. Obstet.* **95,** *155* (*1952*)) reports a series of total body water measurements in patients with various types of illnesses and injuries. As a basis for interpretation of the observed data, Moore and co-workers point out the importance of knowing, approximately, what the "normal" body composition should be for the particular individual under study. Some of the variations to be expected in terms of age and sex have already been discussed. In addition, since within any age group of either sex variations in water content of normal individuals can reasonably be assigned to variations in fat content, they have arbitrarily divided the patients studied by them into six basic body types; males: (1) normal habitus, (2) thin, (3) obese; females: (4) normal habitus, (5) thin, (6) obese. The relation of body water content to body build has been recently discussed (*Nutrition Reviews* **10,** *181* (*1952*))—a high positive correlation between endomorphy ratings and percentage of body fat was observed (C. W. Dupertuis *et al.*, *J. Applied Physiol.* **4,** *364* (*1951*)).

Moore *et al.* indicate that changes in body composition may result from (1) loss or gain of whole tissue, (2) loss or gain of fat, (3)

loss or gain of water, (4) loss or gain of lean tissue, (5) various combinations of these. An estimate of these changes in 25 patients is made by them utilizing measurements of total body water. Their calculations are based on the following assumptions: (1) Lean tissue contains a constant amount of water, about 73 per cent. Based on this, as already mentioned, per cent body fat = 100 − per cent body water/0.732. (2) If body water is unchanged and lean tissue remains constant as measured by nitrogen balance while weight changes, the change in weight is due to a change in the fat content of the body, the fat being anhydrous. (3) The "lean tissue coefficient" for nitrogen is 30; *i.e.*, the change in nitrogen balance multiplied by 30 gives a change in lean tissue mass, or the change in nitrogen balance × 8.1 equals the change in lean tissue (fat-free) solids. Moore and co-workers point out that these coefficients are based on total lean tissues, including bone and are, therefore, high as applied to soft lean tissues in short-term calculations. They also indicate that revision of these figures will probably be necessary as more data are obtained from human histochemical analyses.

The authors are aware of other limitations of the above assumptions—for example, the water content of lean tissue almost certainly changes in patients with severe disturbances in water distribution and balance. To the extent that the water content of lean tissue changes, calculations based on the formula per cent body fat = 100 − per cent body water/0.732 will be in error. Further errors in the calculations will result from changes in relative skeletal weight. Changes in the extracellular:intracellular water ratio are commonly observed in the types of patients studied by Moore *et al.* The effect of changes in this ratio on calculations of body fat has been discussed earlier in this review. Accurate body weight determinations are essential, but, as the authors point out, this may be extremely difficult in the seriously ill patient because of acute changes in hydration and weight within a single day. The presence of dressings, splints, tubes, etc., introduces further inaccuracies.

Total body water measurements and calculated body compositions are reported for 25 patients. Despite the limitations mentioned, certain trends are apparent. The most rapid changes in body composition were those associated with acute disturbances in water balance. Excessive assimilation of water was more common than dehydration. Net water losses exceeding 2000 cc. per day were rarely seen. In addition to the well-recognized nitrogen losses following acute illness or trauma (*Nutrition Reviews* **3,** *40, 86, 253 (1945)*; **4,** *6 (1946)*; **5,** *46 (1947)*; **6,** *20, 161 (1948)*; **7,** *123 (1949)*; **8,** *137 (1950)*; **9,** *257 (1951)*), there is an increased oxidation of body fat. The usual daily rate of fat utilization appeared to be about 75 g., but occasionally was as high as 600 g. The usual daily average postoperative loss of nitrogen was 5 to 7 g., but occasionally a loss up to 25 g. of nitrogen per day was observed. The relative proportions of body fat and lean tissue lost varied from patient to patient; generally in the early period after injury the loss of body fat was usually relatively greater than the loss of lean tissue.

During convalescence, all possible combinations of fat and lean tissue gain were observed. In general, the lean tissue appeared to be gained first, followed later by fat. The convalescent lean tissue gain rarely exceeded a rate of 3 to 5 g. of nitrogen (90 to 150 g. lean tissue) per day. There is usually a concomitant decrease in extracellular water (*Nutrition Reviews* **9,** *299 (1951)*; **10,** *14 (1951)*).

Three patients were studied during periods of effective therapy of thyrotoxicosis. Where the weight loss had not been extensive, the weight gain during recovery was of both body fat and lean tissue in roughly the proportions found in normal subjects.

Three patients with severe burns were studied. The changes in body composition noted in the burned patients were first, a period of water gain (burn edema); next, a period of loss of the burn edema and a long phase of mixed tissue loss, high in fat; and, third, a period of repletion.

The data presented by Moore, Edelman and their associates emphasize again the variations in body composition which occur normally with age and sex. However, considerably more individuals in good health of all ages and both sexes must be studied to establish statistically significant values for normal subjects throughout the life span. Extension of these technics to the study of additional patients is anticipated. Measurements of extracellular fluid as well as of total body water would be useful. Specific tissue studies are needed to establish the variations of lean tissue water content in disease. Histochemical measurements would also provide information about the various organs and tissues individually as opposed to the over-all data provided by the usual balance studies.

TYROSINE METABOLISM ON LOW ASCORBIC ACID INTAKES

Hydroxyphenyl compounds, metabolites of the aromatic amino acids phenylalanine and tyrosine, are excreted in abnormally high amounts by human infants when they are placed on diets deficient in ascorbic acid. This condition is relieved by the administration of ascorbic acid (*Nutrition Reviews* **8,** *260 (1950)*). A similar condition was reported in 2 adults who had scurvy by R. R. Sealock and H. E. Silberstein (*Science* **90,** *517 (1939)*). W. F. Rogers and F. H. Gardner (*J. Lab. Clin. Med.* **34,** *1491 (1949)*) also noted the abnormality when scorbutic adults were given daily doses of 20 g. of tyrosine as a supplement to the diet.

Two laboratories have recently reported on the influence of extended low ascorbic acid intakes in healthy young adult human subjects on the metabolism of aromatic amino acids. Workers at Cornell University (B. F. Steele, C.-H. Hsu, Z. H. Pierce, and H. H. Williams, *J. Nutrition* **48,** *49 (1952)*) studied the excretion of hydroxyphenyl compounds in 10 subjects receiving a diet supplying about 7 mg. of ascorbic acid daily per subject and supplemented with 10 g. of L-tyrosine daily, a dose which is about two and one-half times the normal daily intake. Initial serum ascorbic acid levels (1.1 mg. per cent) indicated that the subjects were in good ascorbic acid nutriture at the start of the experiment. After thirty-one days on the diet the serum ascorbic acid levels had declined to 0.3 mg. per cent and remained fairly constant at this level for the remainder of the seventy-eight-day experimental period.

Despite the rapid decline in serum ascorbic acid levels, there was no indication of an abnormal tyrosine metabolism in these subjects. Initially the urinary excretion of hydroxyphenyl compounds averaged 420 mg. per person per twenty-four-hour period, and after seventy-three to seventy-eight days on the ascorbic acid-low diet, it averaged 431 mg.

There was a trend toward an increase in the reducing power of the urine as the subjects became more deficient in ascorbic acid. Expressed as hydroquinone equivalents, the subjects excreted an average of 110 mg. per twenty-four-hour period initially and 201 mg. at the end of the seventy-eight-day experimental period. These values are considered within the normal range and thus are not indicative of any derangement in tyrosine metabolism.

Workers at Oregon State College (B. L. Davey, M.-L. Wu, and C. A. Storvick, *J. Nutrition* **47,** *341 (1952)*) investigated the influence of an ascorbic acid intake of 25

mg. daily in 4 healthy subjects over a period of fifty-two days. The urinary excretion of hydroxyphenyl compounds (homogentisic acid equivalents) ranged between 55 and 106 mg. among the subjects at the close of the experimental period, compared with a range from 84 to 118 mg. initially. There was thus no indication of disturbed metabolism of aromatic amino acids. The level of ascorbic acid intake in these subjects, 25 mg. daily, was not enough to maintain what are considered good blood levels for normal ascorbic acid nutriture, *i.e.*, 0.6 to 0.8 mg. per 100 ml. of serum. The serum levels had declined from initial levels of about 1.0 mg. per cent to about 0.3 mg. per cent, which appears to equal the level of depletion attained in the Cornell study.

In both the Cornell and the Oregon State studies the dietary intake of folacin was not ascertained. Folacin is known to alleviate hydroxyphenyluria when administered in relatively large amounts (*Nutrition Reviews*, *loc. cit.*).

These studies seem to indicate that within a period of fifty-four to seventy-eight days there is no disturbance of aromatic amino acid metabolism in adult human subjects when blood ascorbic acid levels are reduced to about one-half of what is considered desirable, and when ascorbic acid intake is as low as one-tenth of that recommended, *i.e.*, 75 mg. daily.

INTESTINAL PARALYSIS PRODUCED BY DECREASED INTRACELLULAR POTASSIUM

One of the complications of abdominal surgery which may be of serious import is that of paralytic ileus. Characteristically it occurs three or more days after operation. It is marked by abdominal distension, vomiting and absence of intestinal motility. This condition may occur in man without association with surgical procedures. The causes and mechanisms of production of paralytic ileus are unknown.

Observations have been described which would indicate that abnormalities in concentrations of plasma electrolytes contribute to the occurrence of paralytic ileus. The plasma chloride concentration is often low in this condition. D. H. P. Streeten (*Surg. Gynec. Obstet.* **91,** *421* (*1950*)) noted that recovery occurred in several patients when there was an increase in the excretion of urinary chloride following infusion with saline solution. Furthermore, *in vitro* studies with segments of rabbit, guinea pig, and human intestine immersed in a bath containing a solution with relatively low concentrations of sodium chloride demonstrated that there was reduction in extent of contractions or actual disappearance of them. D. C. Darrow (*New Engl. J. Med.* **242,** *978* (*1950*)) noted the similarity of manifestations in potassium deficiency and in paralytic ileus and suggested that the intestinal paralysis may be caused by a decrease in the plasma content of potassium.

Although frequent association of abnormalities in concentrations of plasma electrolytes in paralytic ileus has been demonstrated, an etiologic role for ionic disturbances has not been established. This problem has been the subject of recent investigations of D. H. P. Streeten and E. M. V. Williams at the University of Oxford (*J. Physiol.* **118,** *149* (*1952*)). Attempts were made to see if intestinal motility might be reduced or abolished by producing a decrease in plasma sodium chloride and to determine other electrolyte changes secondary to salt depletion which might be importantly associated with paralytic ileus.

The investigators utilized a technic for determining intestinal propulsion in iso-

lated loops of jejunum left intact in the abdominal cavity of dogs and with access to the proximal and distal ends of the loop through permanent openings in the abdominal wall (D. H. P. Streeten and E. M. V. Williams, *J. Physiol.* **112,** *1* (*1951*)). The animals were depleted of sodium and chloride by intraperitoneal infusions of a Tyrode solution free of sodium chloride and containing 4.5 per cent dextrose. The infused fluid was withdrawn from the peritoneal cavity after a period of two to four hours. It had been found that this approximate length of time was required for equilibration of electrolyte content in the peritoneal fluid with that of the plasma. A single intraperitoneal infusion of as much as 100 ml. of solution per kilogram body weight caused a loss of from 2.4 to 7.0 g. of chloride and from 0.9 to 3.5 g. of sodium. Infusions were repeated on subsequent days until the plasma chloride had been reduced to the level desired.

The effect of moderate depletion of sodium chloride was to cause an initial increase in the rate of fluid propulsion in the intestinal loop. As the salt deficiency was increased, there was a decrease in the propulsive rate and actual paralysis. Injection of a solution of sodium chloride after intestinal motility had been markedly inhibited resulted in an immediate increase in amplitude of contractions and a gradual return of propulsive force to the intestinal wall.

The depression of intestinal motility was always associated with a decrease in plasma sodium and chloride concentrations. Moreover, there was an increase in levels of plasma potassium. In one animal, for instance, the plasma concentration of potassium was 15 mg. per 100 ml. before infusion and increased to a level of 30.5 mg. per 100 ml. after salt depletion and the occurrence of intestinal paralysis.

The depression of intestinal motility in these salt-depleted animals occurred before there was evidence of respiratory or circulatory embarrassment. However, if depletion was carried further there were secondary effects which endangered the lives of the animals.

Since the depression of intestinal propulsion was found uniformly to be accompanied by an increase in plasma potassium, the authors gave particular consideration to the effect of this cation on intestinal motility. The increase in plasma potassium was observed after intervals of more than an hour following the withdrawal of the intraperitoneal fluid, indicating that the larger quantities of potassium in the plasma may have been derived from sources within cells.

In the effort to determine whether it was the greater concentration of potassium in plasma which is responsible for the effect on intestinal motility, a solution containing 185 mg. of potassium chloride was slowly injected intravenously into a dog which had been moderately depleted of salt. There had been some depression of intestinal propulsion prior to the injection, but propulsion was totally abolished with the added potassium. However, nonpropulsive contractions of the loop persisted. The paralysis with complete atony which occurred in severe salt depletion did not occur after potassium injection. It seemed unlikely, therefore, that the paralytic ileus induced by salt depletion was caused simply by an increase in plasma potassium.

Strips of excised jejunum were suspended and permitted to contract *in vitro* in a Tyrode medium low in content of sodium chloride. After one hour the quantity of potassium in the medium and in the jejunal wall was determined. It was found that there was a significant loss of this electrolyte from the jejunum and an increase in the quantity in the medium. This mobilization of potassium from cells did not occur when intestinal strips were allowed to contract in Tyrode solution containing usual quantities of salt.

Most severe states of salt depletion in

these dogs were associated with an increase in the hematocrit produced by passage of water into red cells and the later occurrence of circulatory collapse. Since these events might lead to tissue anoxia, the motility of jejunal loops was determined as dogs breathed varying concentrations of oxygen. With low oxygen mixtures the tone and motility of the intestine were reduced. It was, therefore, suggested that circulatory failure could have been a contributory factor in development of complete intestinal paralysis after profound salt depletion, but could not have been responsible for the depression of motility after moderate salt depletion.

In view of these findings it may be concluded that depression of intestinal propulsion and perhaps the occurrence of paralytic ileus may be related causally to a reduction in cellular potassium. If these observations are confirmed, therapeutic approaches in the treatment of paralytic ileus should include correction of electrolyte deficiencies and particularly those of potassium.

OBESITY, WEIGHT REDUCTION AND LONGEVITY

Obesity is a subtle but serious health hazard. As a rule, it develops gradually. The psychologic background and motivation resulting in an excessive food intake may vary widely, but food is either a genuine source of pleasure, or it serves as a substitute for other unsatisfied cravings. In either case the dietary treatment, almost unavoidably associated with some discomfort, is likely to be resented by the victim trapped in his or her own fat. A clear understanding of the medical dangers of obesity, in addition to the esthetic impulse, should help to motivate the patient during the course of weight reduction as well as during the subsequent months and years. Persistence in eating a low-calorie diet, nutritionally well balanced, may tax the individual's self-discipline more severely than the heroic but relatively brief period of weight reduction.

Excessive weight becomes a physical impediment in itself. More importantly, it tends to predispose the individual to a variety of "degenerative" diseases and hastens their downward course. The relation of obesity to health and disease was examined by D. B. Armstrong, L. I. Dublin, G. M. Wheatley, and H. H. Marks (*J. Am. Med. Assn.* **147,** *1007 (1951)*; *Nutrition Reviews* **10,** *138 (1952)*). Both the data in the literature and those resulting from a new mortality study, undertaken by the Metropolitan Life Insurance Company, were taken into account.

"Mortality Among Insured Overweights in Recent Years" was examined in detail by L. I. Dublin and H. H. Marks (*Proc. 60th Annual Meeting, Assn. Life Insurance Medical Directors of America, Oct. 11–12 (1951)*). The authors recalled the early days of the insurance business when the hale and hearty stout man was considered a prime candidate for life insurance. A remark by O. H. Rogers, made in 1901, is cited which indicates that there had been a tendency to consider *desirable* a certain degree of hypernutrition. This idea was abandoned as soon as the life insurance physicians and actuaries put the evaluation of life insurance risks on an empiric, medico-statistical basis.

While the investigations reported during the past fifty years were fairly consistent in their findings, a new study of overweight was considered timely. In the last decade or two dramatic changes have taken place in the over-all mortality picture. The steadily declining number of deaths due to infectious diseases, especially tuberculosis and pneumonia, was a particularly important factor. Earlier, these conditions were exacting a higher toll among underweights

and made overweight appear less undesirable. This problem required a re-evaluation.

The study of Dublin and Marks was based on policies issued to overweight whites between the years 1925 and 1934, and followed up to 1950. Excluding cases which could be rated either for other impairments than excess weight, adverse medical history, or occupational hazards, the study covered about 26,000 men and 25,000 women. The deaths recorded down to the policy anniversary in 1950 numbered about 3700 among the men and 2700 among the women. The results were evaluated on the basis of the contemporaneous mortality experience (by age at issue and the duration of the policy) among persons accepted for standard insurance.

Combining men of all ages (20 to 64 years), the mortality from all causes was 150 per cent of the expected value. Interestingly enough, the presence of overweight at younger ages is more hazardous. The percentages of deaths (actual as per cent of expected) for the individuals insured in the third, fourth, fifth, and sixth decade of life were 180, 169, 152 and 131, respectively. For women of all ages the mortality was 147 per cent of the expected, a value very close to that for men. However, there was no definite trend in the mortality ratios according to the age at which the policy was issued. In part, at least, this may be due to the fact that the weight limits for older and younger women were not identical. On the basis of the standards used in evaluating obesity, the degree of overweight permissible within the limits of standard insurance was somewhat greater for women than for men, and for younger persons than for older persons. This fact complicates the interpretation of the data.

Without specifying the respective degrees of overweight, the authors computed the mortality experience in the "Intermediate" insurance class, with expected mortalities varying 30 to 50 per cent above standard, and in the "Special" class with still higher expected mortalities. In the aggregate, the mortality ratios for men in those two groups were 142 and 179 per cent, for women 142 and 161 per cent. Among the markedly overweight men, who were issued the insurance in the third, fourth, fifth and sixth decade of their life, the frequency of deaths corresponded to 231, 220, 172 and 143 per cent of the contemporaneous mortality experience on standard risks. This indicates, again, that overweight constitutes a greater health hazard when it occurs in younger individuals.

The results were tabulated also according to the degree of departure from average weight, without the special considerations resulting from previous life insurance experience and practice. For scientific purposes, this is a definitely preferable mode of analysis. Combining men of all ages and all heights, the overweight of 20, 30, 40, 50, and 60 or more per cent was associated with mortality ratios of 142, 151, 178, 234 and 282 per cent. In women there was also a consistent upward progression of the mortality ratios with increasing departure from average weight, except for the last weight group (139, 148, 156, 175 and 143 per cent of the mortality experience on standard risks).

The mortality comparison by causes of death discloses a pattern established in earlier investigations (*cf.* Armstrong *et al.*, *loc. cit.*). The excess mortality of the overweight individuals was largely accounted for by high death rates from degenerative diseases of the heart, arteries and kidneys (with actual deaths among men equal to 149 and among women 177 per cent of the mortality experience of standard risks) and diabetes (383 and 372 per cent). There was a high relative mortality from gallstones (208 and 284 per cent), appendicitis (223 and 195 per cent), and cirrhosis of the liver (249 and 147 per cent). Incidence of tuberculosis was very low (21 and 35 per cent). Two other causes of death may be noted. While automobile accidents were

higher (131 and 120 per cent) than in the standard group, the incidence of suicide was definitely lower (78 per cent for men, 73 per cent for women).

A particularly interesting phase of the study concerned the mortality experience in individuals who were initially overweight but who subsequently reduced their weight. This placed them either in the "standard risk" category or in a lower-premium, though still "substandard," class. Among men who originally were moderately overweight ("Intermediate" class with mortality equal to 142 per cent of standard) and reduced, the mortality decreased to 113 per cent. In the men who were initially markedly overweight (expected mortality of 179 per cent), mortality of those who reduced their weight was 109 per cent. In women similar trends were observed, but the number of individuals was too small to allow safe generalizations.

The number of long-term studies on the effects of weight reduction is surprisingly small. The present investigation has yielded striking results indicative of real benefits, in terms of longevity, resulting from weight control. The study suffers from important weaknesses, inherent in all insurance statistics, principally the fact that no information is available on the course of the individual's weight following the issuance of the policy. Also, the number of men involved in this particular study was small (129 and 36, in the two weight classes). The effects of weight reduction constitute one of the most urgent research topics in the United States. Further studies, carried out on larger samples, with better means for describing the degree of obesity, and more adequate information on the duration and degree of weight reduction are needed in order to provide a firmer basis for a weight-control campaign.

The desirability of *prevention* of overweight has been clearly demonstrated, in accord with the older and recent studies (*cf.* B. F. Blair and L. W. Haines, *Tr. Actuarial Soc. Amer.* **50**, *Part 1, No. 121, 48 (1949)*; D. N. McCormick, *Ibid., Part 2, No. 122, 200 (1949)*). The association of overweight and degenerative diseases, which are steadily gaining importance as causes of disability and death, seems to have been firmly established on a statistical basis. The mechanisms involved have not been satisfactorily clarified. The fundamental defects are, at least in part, metabolic in nature and must be studied in reference to more direct criteria than height and weight. Such a research as well as the development of more adequate means for the characterization of body build is likely to be carried on outside the framework of life insurance companies.

COMBINED DEFICIENCY OF VITAMIN B_{12} AND FOLACIN IN SWINE

In a study of vitamin B_{12} deficiency a group of swine receiving no vitamin B_{12} failed to develop a macrocytic anemia with a megaloblastic bone marrow. The investigators at the University of Utah thought that the presence of folacin in the diet as a contaminant of soybean protein prevented the development of megaloblastic anemia even in the absence of vitamin B_{12}. Further studies to test this hypothesis are reported by G. E. Cartwright, B. Tatting, D. Kurth, and M. M. Wintrobe (*Blood* **7**, *992 (1952)*). Animals were fed a vitamin B_{12}-deficient diet with vegetable protein, and with a folacin antagonist added to produce the dual deficiency.

Twenty pigs aged 21 to 28 days received the following diet: soybean alpha-protein, 31.2 per cent; sucrose, 37 per cent; lard, 26.6 per cent; and salt mixture #3, 5.2 per cent; plus succinylsulfathiazole, 2 per cent; and a crude methylfolic acid antagonist, 0.4 per cent. The soybean alpha-protein was shown to contain one microgram of fo-

lacin per gram by *Lactobacillus casei* microbiologic assay.

In two to three months an anemia developed that was definitely macrocytic. This anemia was normochromic since there was no reduction in the mean corpuscular hemoglobin. No significant increase in reticulocytes was noted. There was a leukopenia with a greater decrease in polymorphonuclear cells than mononuclear cells. The peripheral blood anisocytosis was marked with many macrocytes.

No neurologic lesions were observed. There was no increase of pigment excretion in the deficient swine, and the feces at all times were dark and semisolid. The pigs appeared unkempt, hair growth was poor, and although large areas of alopecia were not present, small ones did appear.

When vitamin B_{12} supplementation alone was given, there was a rapid moderate increase in reticulocytes with an increase in the volume of packed red cells, but in no animal was the anemia completely relieved. There was no significant increase in leukocytes. Growth was stimulated. The cellularity of the bone marrow increased, then subsided, and its morphology remained like that of swine deficient in folacin.

When a folacin supplement alone was given, there was an immediate return of the blood and bone marrow to normal limits. After several months there was a partial hematologic relapse in spite of continued therapy with this vitamin. Growth of the animal was stimulated. Leukocytes increased, then decreased to pretreatment levels.

When both vitamin B_{12} and folacin supplements were given, the anemia was rapidly and completely relieved. The bone marrow became normal, there was greater growth than with either vitamin alone, and the leukocytes and differential count became normal.

This experimental disorder in swine, the dual deficiency of vitamin B_{12} and folacin, resembles in different degree various conditions now classified as "megaloblastic macrocytic anemias," *i.e.*, the megaloblastic anemia of pregnancy, nutritional macrocytic anemia, tropical and nontropical sprue. In different ways the deficiency in swine lacks important features of human pernicious anemia, especially the development of neurologic changes. The species difference between man and the experimental animals makes it difficult to produce typical pernicious anemia experimentally. Some additional factor or factors may yet be involved in the pathogenesis of pernicious anemia.

DIETARY FAT FOR REPRODUCTION AND LACTATION

The comparative value of fats versus carbohydrates as energy sources in the diet of animals continues to receive the attention of nutritionists. Fundamental information on this question is needed before optimum fat levels in the diet can be established with certainty (*Nutrition Reviews* **10,** *154* (*1952*)). Studies by R. W. Swift and A. Black (*J. Am. Oil Chem. Soc.* **26,** *171* (*1949*)) indicated some definite beneficial effects of dietary fat, as compared to high carbohydrate diets of equal energy content, in the reduction of heat production and heat increment, and in the increased efficiency of food utilization.

More recently workers at Pennsylvania State College have extended these studies to include influences of dietary fat on reproduction and lactation in rats (C. E. French, R. H. Ingram, L. K. Knoebel, and R. W. Swift, *J. Nutrition* **48,** *91* (*1952*)). A complete commercial rat diet was used which upon analysis was found to contain approximately 21 per cent of protein, 4 per cent of fat, and 6 per cent of fiber. The two experimental diets (high-fat and high-

carbohydrate) were prepared by mixing 20 per cent of corn oil or 20 per cent of sucrose with 80 per cent of the basal diet. To insure optimum intakes of all dietary essentials, the experimental diets were also fortified with one per cent each of liver powder and yeast and with the following vitamins (milligrams per 100 g. of diet): choline chloride, 160; alpha-tocopherol acetate, 5; and thiamine hydrochloride, 0.2.

The study extended over a two-year period and measured the relative values of high-fat, high-carbohydrate, and normal diets for reproduction and lactation through three generations. The diets were fed ad libitum. The reproduction studies included 78 matings on each diet and the lactation studies averaged 350 young for each diet. The litter size was reduced to 6 young for measure of lactation performance. The studies were therefore of sufficient magnitude to justify a careful examination of the diet effects.

Since the diets were considered adequate in all dietary essentials, any differences were expected to be small. Nevertheless, two significant results were apparent. Sucrose had a favorable effect on lactation and the high-fat level in the diet had an adverse effect on reproductive performance. Rats on the high-fat diet produced an average of 9.3 live young at birth per litter, the females averaging 5.7 and the males 6.1 g. in body weight. Rats on either the high-carbohydrate diet or the commercial diet produced an average of 10 live young at birth per litter with both the males and females averaging about 0.4 g. more in birth weight than the young from mothers receiving the high-fat diet. The superior lactation performance of rats on the high-carbohydrate diet was evident when the average body weights of the nursing young were compared. The young nursed by mothers on this diet averaged 10 per cent heavier in body weight than those nursed by mothers on either the high-fat or the commercial diet. This difference was evident at 14 days of age as well as at 21 days.

These results are in harmony with those reported by M. L. Meyer, H. T. Thompson, and C. A. Elvehjem (*J. Nutrition* **45,** *551 (1951)*), who observed improvement in reproductive and lactation performance in rats when the fat content of pork-containing diets was reduced either by adding sucrose (diluting effect) or by removal of a portion of the fat. These workers stressed the need for more basic information concerning the influence of the composition of the diet as a whole on the requirements for reproduction and lactation. The importance of this concept was emphasized by the further observation that diets containing sucrose which were relatively adequate for lactation were completely inadequate when the sucrose component was replaced by dextrin. The more favorable influence of sucrose on the intestinal bacteria, which in turn influenced the nutritional requirement of the host, was offered as a possible explanation for this result. If such an explanation is acceptable, it becomes obvious that more attention must be given to the general problem of the influences on intestinal bacteria when dietary carbohydrates are replaced with fat.

The extent to which fats and carbohydrates can be interchanged as energy sources in animal feeds is obviously important, because the extent to which one or the other is in excess supply usually influences its cost.

THE NEED FOR CERTAIN AMINO ACIDS FOLLOWING HEMORRHAGE

It is well recognized that exposure to trauma, with loss of blood, places demands upon the body's store of protein. Recent studies by W. H. Sebrell and E. G. McDaniel (*J. Nutrition* **47,** *477 (1952)*), as an extension of previous work in their laboratory,

indicate that all amino acids may be of some value in blood regeneration following hemorrhage and suggest that certain of the "essential" group may be of particular importance.

These workers used male rats fed a protein-free diet for five days. Daily, for the first four days of the diet, the animals were bled 2 per cent of their body weight, injected intraperitoneally with 0.85 per cent saline before bleeding. On the fifth day blood samples were collected for granulocyte counts, hematocrits, protein and hemoglobin determination. At the end of the period of hemorrhage, the rats were placed on amino-acid test diets. The control group was given all known essential amino acids, including arginine. The remaining 10 test diets were comparable to those given to the control group with the exception that one of the amino acids was omitted and replaced by glucose. The diets otherwise were adequately supplemented with the specific vitamins and excessive amounts of copper and iron. The protein-free ration contained 86.76 per cent anhydrous glucose, whereas the amino acid diet contained only 69.8 per cent glucose, the difference being made up largely by amino acids which totaled 15.41 per cent of the diet so given. The rats were maintained on these various test diets for ten days and were weighed periodically. Studies on their blood were made after four and again after ten days on the various specific amino acid-deficient diets.

Immediately subsequent to the hemorrhage period, all animals were severely anemic. Rats given the ten essential amino acids showed a clear-cut improvement in the criteria studied. All were restored to normal levels after ten days on this control diet, with the exception of the granulocyte count and total body weight. This recovery was most rapid during the first four days following the period of bleeding, save for body weight, which tended to increase most rapidly during the last six-day period on the diet of ten amino acids.

The data showed that each amino acid deficiency had deleterious effects on blood regeneration. These were variable, however, in that certain amino acids seemed more essential for various elements of the blood. Hemoglobin, red cell count and hematocrit were severely depressed when the diets contained no histidine or valine. Leucine and lysine were also of primary importance in red cell and hemoglobin formation. All of these amino acids occur in large amounts in the red cell. The restoration of the granulocyte count toward normal, after hemorrhage, was inhibited chiefly by deficiency in dietary valine with insignificant effects observed after the omission of other amino acids in the food. The hypoproteinemia induced by the procedure was severe, and failed to respond to amino acid diets unless the mixture supplied contained threonine, valine, lysine and tryptophan. Actually, deficiency of any amino acid, with the exception of arginine, leucine, and also methionine in most cases, prevented the normal restoration of serum protein levels.

It was also demonstrated clearly that during the posthemorrhage period each animal lost weight on any (single) amino acid deficiency, with the exception of arginine. As the authors indicate, tissue breakdown products are a possible source of protein for synthesis of hemoglobin (F. S. Daft, F. S. Robscheit-Robbins, and G. H. Whipple, *J. Biol. Chem.* **103,** *495 (1933)*). The animals were said to be losing weight during the regeneration period and hence endogenous protein sources may have influenced the authors' data to a slight degree. It is unfortunate that the authors give no specific information with regard to possible major weight changes in the animals during the period of hemorrhage. A similar factor may also have been in operation during this interval. Also, the relative per cent of amino acids in the diet is certainly not high and it is possible that following a relatively prolonged period of repeated, severe bleeding, other basic needs

for dietary protein or amino acids were considerably elevated. This latter could conceivably greatly influence the degree to which the animal might use exogenous amino acid in relation to the use of acids derived from breakdown of endogenous protein that would not otherwise obtain.

It is apparent, however, that weight loss was a minor factor in the present study. Previous data on rats on a low protein diet (A. Kornberg, *J. Biol. Chem.* **164,** *203 (1946)*; Kornberg, F. S. Daft, and W. H. Sebrell, *Science* **103,** *646 (1946)*) demonstrated that animals fed rations low in casein developed anemia and granulocytopenia and that a mixture of the essential amino acids *in toto* could replace casein. None of these was omitted without resulting impairment in blood regeneration, with the exception of arginine. Survival of this group of animals was poor, perhaps as a result of prolonged protein depletion, and the present method of bleeding during short periods of protein-free diets was inaugurated in order to rule out this possibility.

The present communication is of value not only because it extends and confirms recent work in amino acid deficiency and blood constituents, but also because of the method used to induce anemia. With present world-wide interest in blood loss, because of the problem of hemorrhage and wound shock in combat areas, these observations highlight the need for certain dietary constituents essential to the regeneration, in a relatively specific manner, of certain blood factors. The data reaffirm the need for exogenous protein in periods of blood depletion in order to offer suitable basic constituents to the re-formation of blood elements. It also suggests that specific amino acids might be of value, at least in certain stages, particularly where the bodily stores of endogenous protein amino acids might be depleted by prolonged hardship, with severe subnutritional states. It should be emphasized that the communication in no way implies that these amino acids are the only specific deficiencies which may profoundly influence regeneration of blood elements. The animals studied received an adequate supply of vitamins and other dietary constituents, particularly metals known to be of importance in the formation of blood cellular factors.

ADRENOCORTICAL FUNCTION IN MONKEYS WITH SCURVY

Of all body tissues the adrenal cortex may contain the greatest concentration of ascorbic acid. In addition it has been repeatedly observed that stressful situations of many types and the administration of adrenotrophic hormone (ACTH) produce a decrease in the ascorbic acid content of the adrenal. These and other observations have seemed to give substance to the point of view that this vitamin is importantly concerned in the maintenance of normal function of the adrenal cortex (*Nutrition Reviews* **3,** *37 (1945)*; **8,** *52 (1950)*).

Determination of the quantity of 17-ketosteroids excreted in the urine permits gross evaluation of the level of function of the adrenal cortex, particularly in immature animals and in females in which the amount of these steroid compounds excreted depends largely on the activity of this gland. It was demonstrated by S. Banerjee and C. Deb (*J. Biol. Chem.* **194,** *575 (1952)*; *Nutrition Reviews* **10,** *253 (1952)*) that female guinea pigs fed a diet deficient in ascorbic acid excreted smaller quantities of 17-ketosteroids in the urine than did control animals. This finding was interpreted as indicating that scurvy is associated with hypoactivity of the adrenal cortex. However, it should be pointed out that the

greatest reduction of 17-ketosteroid excretion occurred in animals with fully manifest scurvy, at which time the quantity of 17-ketosteroids excreted was but a third lower than that of control animals.

A similar type of investigation with findings which do not conform with the interpretations of Banerjee and Deb (*loc. cit.*) has been undertaken in monkeys and recently reported by C. T. Stewart, R. J. Salmon, and C. D. May (*J. Lab. Clin. Med.* **40,** *657 (1952)*). Immature animals were used in these experiments. The monkeys were fed a diet of reconstituted dried cow's milk which was boiled with copper sulfate to destroy all traces of ascorbic acid. The milk diet was supplemented with iron, vitamins A, D, and E, as well as with members of the B-complex group of vitamins. A group of control animals was fed the same diet, but in addition was given 50 mg. of ascorbic acid daily. The urine of all animals was collected in twenty-four-hour specimens and the quantity of 17-ketosteroids excreted was determined. Rates of excretion were measured both with and without stimulation of the adrenal cortex with ACTH. ACTH was given in doses of 10 mg. twice daily for three successive days by the intramuscular route. In addition the number of circulating eosinophils in the peripheral blood was counted at intervals with animals in the fasting state. The concentration of ascorbic acid in adrenals and livers was determined on specimens obtained by biopsy, or when animals were killed at the conclusion of the experiment.

Monkeys on the ascorbic acid-deficient diet showed first signs of deficiency after about thirty days when there was loss of vigor and failure to gain weight. Fully manifest scurvy occurred after about eighty days on the diet. Tissue levels of ascorbic acid were markedly reduced by the thirty-seventh day, at which time the liver content of the vitamin was 12.9 mg. per 100 g. wet weight in control animals and 1.2 mg. per 100 g. in monkeys on the scorbutic diet. A similar comparison of ascorbic acid in adrenal tissue showed 50 mg. and 5 mg. per 100 g. wet weight in control and deficient animals respectively. There was but slight further reduction in concentration of ascorbic acid in these tissues after manifestations of scurvy had occurred.

There were important and significant changes in the spontaneous rate of urinary excretion of the 17-ketosteroids in the deficient animals. The mean rate of excretion was 0.34 mg. per kilogram of body weight per twenty-four hours in monkeys on the control diet. The rate was reduced by about a third after four weeks on the scorbutic diet and persisted at this low level until signs of scurvy appeared. The lowest rate of excretion was about 0.20 mg. per kilogram per twenty-four hours, and the difference from control rates of excretion is statistically significant. It is of interest that this reduction is comparable to that observed in guinea pigs with scurvy by Banerjee and Deb (*loc. cit.*). However, it was also observed that the spontaneous rate of excretion of 17-ketosteroids increased as the manifestations of scurvy appeared and tended to equal or exceed that of control animals. This would seem to indicate unimpaired function of the adrenal cortex in scurvy. The authors also determined the spontaneous rate of excretion of 17-ketosteroids in a monkey of similar age in which total adrenalectomy had been done. The excretion rate in this animal averaged 0.13 mg. per kilogram per twenty-four hours, a rate much below the lowest rate determined in monkeys on the deficient diet.

Stimulation of adrenocortical activity by injection of ACTH produced a five- to tenfold increase in the quantity of 17-ketosteroids excreted in deficient as well as control animals. The total quantity excreted under the stimulus was similar in control, deficient and scorbutic monkeys. In contrast, no increase in the urine content of 17-keto-

steroids occurred when ACTH was administered to the adrenalectomized animal. Again this evidence indicates normal response of the adrenal cortex in monkeys with ascorbic acid deficiency.

The number of circulating eosinophils in the blood of ascorbic acid-deficient animals was frequently reduced and in monkeys with scurvy was often found to be markedly decreased. This finding suggests increased adrenocortical activity in scurvy. However, the authors are not willing to accept totally this interpretation, since they also observed that there was marked depression of eosinophils in the adrenalectomized control animal at the time of a wound infection. It is their belief that factors other than adrenocortical activity may act to cause a decrease in circulating eosinophils.

These observations provide important considerations in evaluation of the mass of experimental data which has accumulated pertaining to the role of ascorbic acid in adrenocortical function. Under the conditions of these experiments it is impossible to conclude that ascorbic acid deficiency leads to depression of activity of the adrenal cortex. The findings are in line with those of other investigators. B. E. Clayton and F. T. G. Prunty (*Brit. Med. J.* **2,** *927* (*1951*)) observed an increase in the spontaneous urinary excretion of 17-ketosteroids with the onset of scurvy in guinea pigs. Determination of the formaldehydegenic steroids in the urine is perhaps a more direct measure of adrenocortical hormones excreted than is the 17-ketosteroid fraction. E. M. Nadel and J. J. Schneider (*Fed. Proc.* **11,** *263* (*1952*)) found a marked increase in the excretion of formaldehydegenic steroids by scorbutic guinea pigs. In addition, A. B. Eisenstein and R. E. Shank (*Proc. Soc. Exp. Biol. Med.* **78,** *619* (*1951*)) provide evidence that ascorbic acid deficiency functions as a nonspecific form of stress and that this vitamin is not directly involved in mechanisms of elaboration of biologically active adrenal cortical hormones in guinea pigs. The sum of the accumulated evidence would seem to warrant the view that ascorbic acid deficiency does not significantly depress adrenocortical activity or inhibit the response of this gland to various types of stimulation.

HYPERCHOLESTEROLEMIA WITH FAILURE TO INDUCE ATHEROSCLEROSIS IN THE RAT

In the study of the nutritional and metabolic factors which relate to the occurrence of atherosclerosis, experimental animals of several species have been utilized. The inclusion of large quantities of cholesterol in the diet has been demonstrated to produce atherosclerosis in rabbits, chickens, hamsters, and guinea pigs (*Nutrition Reviews* **8,** *74* (*1950*); **9,** *295* (*1951*)). Dogs and rats have proved more resistant to the development of this lesion. However, it has been possible to induce atheromata in dogs by feeding large amounts of cholesterol when these animals were made hypothyroid through the expedient of simultaneous feeding of thiouracil (A. Steiner, F. E. Kendall, and M. Bevans, *Am. Heart J.* **38,** *34* (*1949*)). The greater resistance of rats to the development of arterial lesions is attested to by the failure of cholesterol and thiouracil feeding to produce typical lesions, although this procedure effects a two- to three-fold increase in blood cholesterol (L. Horlick and L. Havel, *J. Lab. Clin. Med.* **33,** *1029* (*1948*)).

I. H. Page and H. B. Brown have recently published the results of experiments in which additional attempts were made to induce hypercholesterolemia and atherosclerosis in rats (*Circulation* **6,** *681* (*1952*)). These observers approached the study of this problem on the premise that aortic

and coronary atherosclerosis might conceivably be produced if serum cholesterol concentrations could be elevated and maintained for long periods of time at values as high as or higher than those which elicit arterial lesions in rabbits, chickens and dogs. A variety of methods were tried in the effort to achieve marked degrees of hypercholesterolemia. The most successful procedure seemed to be one combining hypothyroidism and the feeding of cholesterol and cholic acid.

The animals utilized were adult rats of both sexes. They were made hypothyroid by injection of one microcurie of radioiodine. Basal diets were of two types—either a laboratory dog chow or a modified Sherman ration. Cholesterol was fed at a level of 4 per cent and cholic acid at a level of 2 per cent of the diet. Blood samples were obtained at intervals of three to four weeks. Surviving animals were killed after eight months, or after longer intervals in some experiments. Blood was obtained at this time for determination of lipoprotein fractions by use of the ultracentrifuge. Gross and histologic studies were done on heart, aorta, kidneys and liver.

It was found that either basal diet supplemented with cholesterol or with cholic acid failed to cause any great increase in serum cholesterol in normal or euthyroid animals. Diets containing supplements of cholesterol plus cholic acid brought about a two and one-half- to five-fold increase in the control cholesterol levels of groups of normal rats. In contrast, in animals made hypothyroid by prior injection of radioiodine, there was an even more pronounced effect of feeding cholesterol and cholic acid. Serum concentrations of cholesterol were increased eight- to fifteen-fold. Mean values were about 700 and 1500 mg. per cent respectively in groups of hypothyroid rats fed laboratory chow and the modified Sherman diet plus both supplements. These levels compare with serum cholesterol concentrations of approximately 100 mg. per cent in hypothyroid animals which were not given the supplement of cholesterol plus cholic acid. The degree of elevation in serum cholesterol achieved is similar to that observed in animals of other species in which atherosclerosis has been induced.

The data recorded also demonstrate that hypothyroidism or cholic acid treatment alone is without effect on serum cholesterol. Although dietary supplements of cholesterol without addition of cholic acid fed to hypothyroid rats did produce some elevation in serum cholesterol levels, the increase was but a fraction of that obtained when both supplements were included in the diet.

The investigators determined the quantities of a number of lipoprotein fractions contained in the serum of rats from the various experimental groups with ultracentrifuge technics. The concentration of alpha- and beta$_1$-lipoproteins which occur in the serum of normal rats was not grossly changed under the conditions of these experiments. However, new fractions appeared, one of which was similar to that of the S_f 12 to 20 class described as associated with atherosclerosis by J. W. Gofman *et al.* (*Circulation* **2,** *161* (*1950*); *Nutrition Reviews* **9,** *167* (*1951*)). These lipoproteins were present when cholic acid alone was fed as a supplement, but concentrations were two to three times greater when cholesterol alone was fed. Still higher levels were found when the combined supplement of cholesterol and cholic acid was administered.

The conditions found to prevail when hypothyroid rats were fed cholesterol and cholic acid are precisely those observed in other species in which atherosclerosis has been induced. Specifically, this included sustained severe hypercholesterolemia, with appearance of relatively large quantities of beta-lipoproteins, including those of the S_f 12 to 20 class. However, atheroma were not found in the arteries. The intima of the aorta did exhibit large and diffuse accumulations of lipid particles, which were found on occasion to be invading the media. There

were no foam cells to be seen, nor was there evidence of intimal proliferation—histologic manifestations of developing atherosclerosis. The coronary arteries were similarly infiltrated with lipid, but showed no atheromata.

It is the lack of development of atherosclerosis in these experiments with rats which is of greatest interest. Conditions had been established which in other animal species have resulted in the development of typical lesions. Although animals were kept on the high cholesterol-cholic acid diet for periods of eight months and longer, one wonders whether a still longer period might have finally produced atheromata. Again the data do not indicate how soon in the period of feeding serum cholesterol values were increased to the very high levels recorded, or how cholesterolemia might vary in individual animals during the course of these experiments. The authors state their opinion that the most important considerations are those which pertain to the receptivity and response of tissues to lipid. In earlier experiments it had been found that feeding of organic iodide compounds prevented deposition of lipid in tissues and atherosclerosis (I. H. Page and W. G. Bernhard, *Arch. Path.* **19,** *530 (1935)*). The later experiments provided conditions under which there was widespread infiltration and accumulation of fat in susceptible tissues. However, endothelial hyperplasia, foam cells and fibrosis were not produced in arterial walls.

It is suggested that the rat offers opportunities for the study of variables which determine the response of tissues to infiltrating fat. Other investigators have apparently succeeded in establishing conditions under which the tissue response is more complete and results in atheromata. R. W. Wissler, M. L. Eilert, M. A. Schroeder, and L. Cohen (*Fed. Proc.* **11,** *434 (1952)*) describe atheromatous lesions of the coronary and renal arteries, as well as of the aorta, in "middle-aged" obese rats fed a synthetic ration modeled after the diets of patients who developed coronary thrombosis at an early age. The number of animals with such lesions was increased when vascular hypertension and severe hypercholesterolemia were induced. It is to be hoped that these observations will be published in greater detail so that the factors of age, diet and blood pressure may be more adequately evaluated, since experience of the past has uniformly shown the rat to be peculiarly resistant to atherogenesis.

GLYCOGEN

Exactly one hundred years ago—in 1853—the doctorate thesis of Claude Bernard describing the "internal secretion" of the liver opened the era of modern physiologic chemistry. Besides corroborating previous announcements of his discovery of the "hepatic sugar," Bernard described in this historic opus the quantitative influence of the state of nutrition, the nature of food, exercise, age and other factors on the rate of synthesis and of disappearance of liver glycogen. From that time onward progress in our knowledge of the metabolism of glycogen has been symbolic of progress in physiology and biochemistry. Yet knowledge of the structure of the compound, whether found in liver or in muscle, or that of related compounds such as the vegetable amylopectins, progressed relatively slowly.

The studies of Haworth, Meyer, the Coris and other workers suggested that glycogen and amylopectin are branched polysaccharides. The linear portion appeared to be made up of 1–4 linked glucose residues. Inner chains are linear portions situated between two branched points (glucose units

in 1–6 linkage), while outer chains have a branch point at one end and the nonreducing group at the other end.

Three general models have been proposed to represent the structure of the branched polysaccharides of the starch glycogen class. That of H. Staudinger and E. Husemann (*Ann. d. Chem.* **527,** *195* (*1937*)) was a comb-like structure; each side branch originated from a single main branch. W. N. Haworth's (*Chem. Ind.* (*London*) **17,** *917* (*1939*)) model was a laminated structure in which each branch arose from a preceding branch. The latest model was proposed by K. H. Meyer and his collaborators (*J. Phys. Colloid Chem.* **53,** *319* (*1949*)). These investigators visualized an irregular, tree-like structure. They based their reasoning on the fact that the action of beta amylase on polysaccharide conforming to the other models, Haworth's in particular, would yield elongated, thread-like molecules which, on acetylation, could be expected to yield elastic films. Such acetylated derivatives, in fact, were not film-like and this circumstantial evidence argued against the idea that comb-like or laminated models were adequate representations.

Fuller proof of the structure of the glycogen molecule was, however, still needed. Impressive evidence has now become available from the work of B. Illingworth, G. T. Cori and their collaborators, demonstrating that glycogen and amylopectin have multibranched, tree-like structures. In addition, the St. Louis workers were able to determine the degree of branching of glycogen and amylopectins of various origins, and used their technics in the study of a puzzling pathologic entity, von Gierke's glycogen storage disease.

In an early report, B. Illingworth, J. Larner, and G. T. Cori (*J. Biol. Chem.* **199,** *631* (*1952*)) applied enzymatic methods to the determination of chain length in liver glycogen obtained from rats of two strains, dogs, cats, fetal, newborn and adult guinea pigs, fetal sheep and adult rabbits in various nutritional states. Glycogen from tubercle bacillus, earthworm, muscle, horse, rabbit and human muscle was examined. Amylopectin from immature, mature and overmature corn and from potato was also studied. Illingworth and her co-workers used amylo-1,6 glucosidase to split off as free sugar the glucose residues in alpha 1,6 linkage. All other glucose units can be split off as glucose-1-phosphate by the action of phosphorylase. Two independent chemical methods, one based on methylation and one on periodate oxidation, afforded excellent checks of the enzymatic method.

It was found that a fairly continuous series of branched polysaccharides could be demonstrated. The range of the average outer chain was found to be from 7 to 13 glucose residues, that for amylopectins 13 to 16. The average inner chain length is shorter in all cases, ranging from 3 to 5 glucose units for glycogens and from 5 to 6 glucose units for amylopectins. The per cent end group (characteristic of the degree of branching) for different glycogens varied from 8.3 to 5.8 and that for amylopectins from 5.9 to 4.1.

More unexpected than interspecies differences, significant variations were found in per cent end group in the same species, depending on experimental conditions. It was 8.3 in glycogen isolated from fasted rabbits, 6.8 in glycogen obtained from well-fed animals and 6.0 in glycogen freshly deposited after a fasting period. The finding that glycogen structure differs in postprandial or fasting conditions appears of great potential physiologic significance, in that it may in turn affect rates of release of glucose and hence various "glucostatic" mechanisms. Differences were also found between guinea pig liver glycogens corresponding to various stages of development and between corn amylopectin corresponding to various degrees of ripeness.

The same technics of enzymatic degradation were applied in a systematic fashion by these workers (J. Larner, B. Illingworth,

G. T. Cori, and C. F. Cori, *J. Biol. Chem.* **199,** *641* (*1952*)) to rabbit liver and muscle glycogen and to wheat and corn amylopectin, in such a way that the action of amylo-1, 6 glucosidase and of phosphorylase could be alternated until about 90 per cent degradation had been realized. The limit dextrins formed by phosphorylase were isolated after each successive cycle of enzyme action. These successive dextrins were found to be similar in structure as shown by results of enzymatic analysis. As enzymatic breakdown proceeded, the per cent of total branch points decreased in each one of the fragments as the degradation progressed toward the reducing end. Larner and his collaborators concluded that only the tree-like, multibranched model of Meyer could give adequate representation for such a type of degradation.

In another report, B. Illingworth and G. T. Cori (*J. Biol. Chem.* **199,** *653* (*1952*)) describe the results of similar structure analysis of glycogen isolated from the livers of 10 children with von Gierke's disease. Degree of branching and length of inner and outer chains were determined. Stepwise enzymatic degradation was carried out in 2 cases. It was found that in 8 out of the 10 cases no abnormality of glycogen structure could be detected. In one case, however, where the glycogen storage disease affected both liver and skeletal muscle, the liver glycogen had very short outer branches and the muscle glycogen had almost none; the latter resembled the "phosphorylase limit dextrins" of enzymatic degradation studies. In another case, the liver glycogen was less branched and had longer inner and outer chains than normal glycogen. The polysaccharide resembled amylopectin in these properties. The solubility, x-ray diffraction pattern and absorption spectrum of the iodine complex was also more starch-like than glycogen-like.

In 6 of these cases of von Gierke's disease, the glucose-6-phosphatase activity was determined (G. T. Cori and C. F. Cori, *J. Biol. Chem.* **199,** *661* (*1952*)). This enzyme, normally present in the liver, hydrolyzes the glucose phosphate formed by the action of phosphorylase on liver glycogen and releases glucose into the circulation. It was found that in 2 fatal cases the enzyme was practically absent; this could not be explained by the presence of an inhibitor or by the lack of co-factors. The absence of other glycogenolytic enzymes was ruled out as a limiting factor. It was also found that in 2 out of 4 surviving cases of von Gierke's disease with mild symptoms, the activity of the specific phosphatase was below the level found in other liver diseases. Thus the 2 cases with abnormal glycogen structure described by Illingworth and Cori point to different kinds of enzymatic deficiency and emphasize the fact that there are different types of glycogen storage disease. In the fatal cases studied by Cori and Cori, the nature of the deficiency has been clearly identified as one of glucose-6-phosphatase.

This series of papers represents a fine illustration of the extension of fundamental chemical studies to an understanding of human disease processes.

PROTEIN INTAKE AND STARVATION-INDUCED ENDOCRINE INVOLUTION

Starvation produces important changes in the endocrine glands of the rat. With prolonged underfeeding a decrease in the weight and function of all the endocrine glands has commonly been observed. The evidence presented by M. G. Mulinos and L. Pomerantz (*J. Nutrition* **19,** *493* (*1940*)) indicates that the general endocrine atrophy may be secondary to specific failure of the anterior pituitary to secrete its trophic

hormones. When food intake is abruptly stopped the endocrine alterations have been found to be somewhat different. In the rat, adrenal hyperplasia rather than atrophy occurs (Mulinos and Pomerantz, *Am. J. Physiol.* **132,** *368 (1941)*; A. T. Cameron and J. Carmichael, *Canad. J. Res., Section E* **24,** *37 (1946)*).

J. Rivero-Fontan, K. E. Paschkis, E. West, and A. Cantarow (*Endocrinology* **51,** *100 (1952)*) have attempted to determine whether the endocrine effects of starvation are dependent on simple caloric restriction or on the low level of dietary protein. A control group of rats of both sexes was fed a diet with a protein content of 16 per cent. A low protein starvation group was fed 25 per cent of the diet given to the control group. A third group of rats also received only 25 per cent as many calories as the control group, but the protein content of the diet was augmented so that it equalled that of the control group.

After ten days of caloric restriction body weight decreased between 30 and 34 per cent. There was no significant difference between the weight loss of males and females or between rats with "high" and "low" protein starvation diets. The pituitaries of the female rats were less than half their original weight after caloric restriction. The pituitaries of the males decreased relatively less in weight. The thyroid and gonadal weights also showed substantial reductions. The adrenal glands did not participate in the atrophy which involved the other endocrine organs. All starved animals had adrenals which weighed approximately the same as the controls. The authors were unsuccessful in detecting any difference in the weights of the various endocrine glands of the rats fed the "high" and "low" protein starvation diet.

The uptake of I^{131} by the thyroid gland was measured in the three groups of rats. The total uptake of radioiodine was depressed equally in rats of both sexes on the two starvation diets. The decreased uptake could not be accounted for solely on the basis of a decrease in thyroid mass because there was a significant drop in the number of counts per second per milligram of thyroid in all but the female rats fed the high protein diet. The decreased thyroid function observed was interpreted as being due to a reduction in the level of thyrotropic hormone in the blood. Direct evidence for such a decline has been obtained by S. A. D'Angelo (*Endocrinology* **48,** *341 (1951)*). This author assayed the serum obtained from starved rats and mice for thyrotropin using the stasis tadpole technic. The thyrotropic activity of the serum of starved rats was less than that of fed rats but still greater than that of hypophysectomized rats.

Although the gonads of rats fed the "high" protein or "low" protein starvation diets did not differ significantly in weight, a difference was noted in the weights of the uteri and seminal vesicles. The weights of these target organs were significantly greater in those rats ingesting the starvation diet of higher protein content.

Rivero-Fontan and co-workers have analyzed the weights of the endocrine glands in terms of body weight to determine whether the weight changes are proportional to the loss of total body weight. In comparing their results with those of others they observe that undue emphasis has been placed on relative weights. The loss of body fat is largely responsible for the total weight loss. They conclude that only to the extent to which weight loss is due to the catabolism of cellular protein, could one expect the thyroid, for example, to participate in the general pattern of the body.

It is evident that protein restriction is not primarily responsible for the involution of the endocrine organs during chronic underfeeding. The observations reported confirm and extend previous studies of the endocrine sequelae of starvation.

CHOLESTEROL SYNTHESIS FROM ACETATE IN DIABETES

The association of diabetes with hypercholesteremia and atherosclerosis is well known (*Nutrition Reviews* **9,** *167 (1951)*). The mechanism underlying this correlation is, however, still unknown. Two recent reports, dealing with two different types of experimental diabetes, demonstrate that, in both cases, the rate of synthesis of cholesterol from acetate is increased.

The hereditary obesity-diabetes syndrome of mice has been described previously (*Nutrition Reviews* **10,** *303 (1952)*). It is characterized by a body weight three or four times the normal adult limit, an insulin-resistant type of hyperglycemia, glucosuria, a somewhat increased food intake, and no increase in over-all oxygen consumption over the normal value. Serum cholesterol values are high. The primary biochemical block seems to be a reduced capacity to oxidize acetate (K. Guggenheim and J. Mayer, *J. Biol. Chem.* **198,** *259 (1952)*; *Nutrition Reviews* **11,** *88 (1953)*). The diabetes appears to be due to great sensitivity to growth hormone secondary to this block (Mayer, *New Engl. Med. Center Bull.* **14,** *43 (1952)*). When the same amount of radioactive acetate is injected into obese and nonobese mice, it is found that obese animals retain more of the injected acetate than do the nonobese. If obese and nonobese animals are pair-fed for three days and receive with their food the same amount of acetate, it is found that obese mice not only incorporate a much greater proportion of the ingested acetate into fatty acids, but also that the amount of cholesterol synthesized from acetate is greater.

S. Hotta and I. L. Chaikoff (*J. Biol. Chem.* **198,** *895 (1952)*) studied the rate of cholesterol synthesized from labeled acetate by liver slices obtained from normal and diabetic livers. The diabetes was induced by alloxan treatment, which causes an insulin-sensitive type of diabetes by destruction of the beta cells of the pancreatic islets (*Nutrition Reviews* **9,** *82 (1951)*). After the presence of diabetes was established, 5 of the diabetic rats were given insulin and maintained for several days, as were the diabetic animals and normal controls, on a low fat, high carbohydrate diet. All animals were then killed, the livers were quickly excised, and liver slices were prepared, weighed and incubated with labeled acetate. The cholesterol formed was isolated and its radioactivity determined. Production of labeled carbon dioxide was also measured.

Hotta and Chaikoff found that in alloxan diabetes oxidation of labeled acetate proceeds in the alloxan-diabetic liver slightly faster than in the normal liver. This confirms in part the conclusion of Guggenheim and Mayer that while in insulin-resistant diabetes the biochemical block was in the oxidation of acetate, in alloxan diabetes it was in the transformation of pyruvate to acetate and fatty acids. Hotta and Chaikoff found, furthermore, that incorporation of acetate into cholesterol was increased in the "alloxan diabetic" livers to a considerable degree. Insulin reduced acetate incorporation into cholesterol. The order of significance between rates of incorporation corresponding to organs of alloxan-diabetic and of normal animals was high. By contrast, in the obese-hyperglycemic syndrome, Guggenheim and Mayer had found that rates of cholesterol synthesis between normal and obese animals were less significant than those relating to fatty acid synthesis.

A study of the factors controlling the rate of synthesis of cholesterol is indispensable to the understanding of the etiology of vascular degeneration, in diabetes as well as in other physiologic or pathologic states. Present availability of radioactive and heavy isotopes affords powerful research tools which should make possible rapid progress toward solution of this important problem.

NOTES

Letter to the Editor

Dear Sir:

I was interested to read the review in your November 1952 number (**10,** *337 (1952)*) on "Urban Food Consumption in France and in Great Britain." In it you have suggested both the French and the British calcium consumption in 1948 to be about 30 per cent below the "recommended dietary allowance" of the Food and Nutrition Board. As the figure you quote for British calcium consumption is considerably below that recorded in the Ministry of Food National Food Survey for the urban working class population during ten months of 1948, I thought I should bring this latter estimate to your notice.

The technic adopted in the National Food Survey and its results for the years 1940 to 1949 have been published. During 1948, 5623 households containing 20,178 persons were surveyed over ten months (excluding February and March) and their total calcium consumption was found to be just over 1 g. per head per day. This was made up as follows:

	g. calcium per head per day
From milk and cheese	0.49
bread and flour	0.32
vegetables	0.06
other foods	0.14
Total	1.01

I should, perhaps, explain that the high contribution from bread and flour results from the fortification of all national flour with 14 ounces of calcium carbonate per 280-pound sack of flour. If this added calcium is excluded, the total becomes 0.69 g. per head per day, which is very near the 0.67 g. quoted in your review.

It is possible that in the nutrient analysis of the Oxford Institute of Statistics survey the addition of the full quantity of calcium to flour was not included and that certain other items in the diet (*e.g.*, school milk) were also excluded.

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Letter to the Editor

Dear Sir:

Dr. J. R. Smith, in his most interesting discussion of salt (*Nutrition Reviews* **11,** *33 (1953)*) mentions the observation that herbivorous animals frequent salt licks, and that primitive man may have first found sources of sodium chloride by following animals to these salt licks.

This reminds me that I once had occasion, out of curiosity, to examine soil from numerous of these wild animal licks in the Rocky Mountains of Montana. For this purpose I arranged with forest rangers to send me samples of the mud from the many localized spots where the wild forest animals congregated from far and wide to lick the soil.

Although all of these sites were known as "salt licks" the one chemical property they all had in common was complete absence of sodium chloride. A few samples contained traces of soluble iodides, and hence were of obvious value in a geologic formation almost completely devoid of iodine. But the majority of the samples, when tested in an apparatus intended for measuring the salinity of soils by conductivity, showed almost zero conductivity, indicating the absence of any soluble electrolyte which could have explained the animals' predilection for eating such substances.

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Letter to the Editor

Dear Sir:

I hope it is not too late to comment on the review of the article of D. B. Armstrong, L. I. Dublin, G. M. Wheatley, and H. H. Marks (*J. Am. Med. Assn.* **147,** *1007 (1951)*) that appeared in *Nutrition Reviews* for May 1952 (**10,** *138 (1952)*), under the heading "Obesity." The interpretation of correlations between overweight and mortality, and between overweight and the incidence of various cardiovascular diseases, diabetes, gallbladder disease, certain types of cancer and arthritis, kidney impairment, etc., is not so simple as the medical man assumes. In the first place, weight records in insurance statistics are taken at the time of application for a policy, and the causes of death when the policy becomes a claim. In the records discussed by Armstrong *et al.*, the average time interval between the two records was 11.0 years for males and 11.6 years for females (information obtained from H. H. Marks, one of the authors of the paper). What happened to body weight in these intervals is not known.

The most serious objection, however, pertains to the interpretation of a correlation as always demonstrating a direct causal relationship. In the cases under consideration the authors go further than this and designate obesity as the cause, either directly or by implication. As a matter of fact, both the disease and the obesity may be correlated in their occurrence because of a common cause, such as a common hereditary trait. Thus, discussing the association of obesity and diabetes, E. Geiger (*J. Am. Dietet. Assn.* **28,** *905 (1952)*) points out that a causal relation has not been established since only about 5 per cent of obese people develop diabetes. In his words: "Diabetes and obesity may be parallel symptoms of the same basic degenerative disturbance."

If such indirect causal relations exist between obesity and various diseases, then such diseases cannot be described as "penalties of obesity," and their remission or alleviation cannot be expected as a result of weight reduction, whatever other benefits of weight reduction may ensue. Armstrong and his colleagues recognize this weakness in their argument by admitting that "... we lack properly controlled studies to show whether or not the benefits of weight reduction in terms of health and longevity are as real and substantial as they are assumed to be." It seems important that this weakness be emphasized, and that the hope of obese people that weight reduction is the solution of their health troubles may be a vain one.

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Third Survey of Food and Nutrition Research in The United States

About 3000 research projects have been listed to date in the third survey of food and nutrition research being conducted by the Food and Nutrition Board of the National Research Council. The cooperation of academic, governmental, and industrial research organizations in supplying this information has been excellent. July 1 has been set as the deadline for receipt of information. In the forthcoming publication, the project titles will be arranged in eleven sections: Nutritional Requirements, Digestion and Metabolism, Nutritional Deficiencies, Nutrition Surveys, Methodology Pertaining to Nutrients, Enzyme and Hormone Chemistry, Food Composition, Factors Affecting Nutritive Value, Microbiology, Food Acceptance, Nutrition Education. A register of workers in this field, a list of organizations conducting and/or supporting the research, and a subject index will be included. A new feature will be the inclusion of suggested food and nutrition research projects in areas where further work is indicated.